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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,594	06/22/2000	Irina Nazarenko	0942.4980002/RWE/SEZ	8750

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,594	NAZARENKO ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-15, 17-22, 20-22, 47, 59, 63-67 and 76-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15, 17-22, 20-22, 47, 59, 63-67 and 76-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 22, 2005 has been entered.

Status

2. Claims 10-15, 17-22, 20-22, 47, 59, 63-67 and 76-85 are pending.

Claims 10-15, 17-22, 20-22, 47, 59, 63-67 and 76-85 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Interpretation

3. The claims have deleted the negative limitation excluding FRET, and have indicated that the oligonucleotides "are labeled with only a single type of detectable label". A review of the specification finds no specific definition for this phrase. Therefore, in order to properly apply the prior art, the term "single type of detectable label" must be interpreted. Two different molecules which are involved in fluorescent detection are both the same "type" of label since both share similar uses. Without any limiting definition for what constitutes a "single type", any two molecules which share some similarity in use or structure are a single type. The labels of Tyagi share a

common use, in fluorescent assays, and therefore are a "single type" of label. In fact, Tyagi provides further teaching of a "single type" label noting "A second fluorophore that does not form a FRET pair with the first fluorophore can be used in place of a quencher." This is an express teaching to use two fluorophores, which are both a "single type" of label, a fluorophore (see column 8, lines 55-56). A similar interpretation can apply to Nazarenko.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 10-15, 17, 20-22, 47, 59, 76, 78, 80, 81, 83 and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Tyagi et al (U.S. Patent 6,150,097).

Tyagi teaches a method of claims 10, 20, 47 for quantification of target nucleic acid molecules in a sample comprising hybridizing labeled oligonucleotides with the target molecules and quantifying the amount of the target nucleic acid molecules (see column 9, lines 31-57),

Wherein said one or more oligonucleotides comprise one or more detectable labels located only internally (see column 7, lines 23-30, where Tyagi states "another

configuration that should be useful is to separate the label moieties by five nucleotides along the stem hybrid")

Where the labels are a single type of label since Tyagi notes "A second fluorophore that does not form a FRET pair with the first fluorophore can be used in place of a quencher." This is an express teaching to use two fluorophores, which are both a "single type" of label, a fluorophore (see column 8, lines 55-56).

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 5 and example 3)

Wherein said detectable change is not the result of a fluorescence resonance energy transfer (see column 5, lines 56-62 and title "Nucleic acid probes having Non-FRET fluorescence quenching").

With regard to claims 11-12, 14-15, Tyagi teaches placement of the Non-FRET molecular beacons in a PCR amplification reaction and measurement during the PCR reaction(see column 14, lines 19-62).

With regard to claims 13, Tyagi teaches fluorescent labels (see Table I, column 6).

With regard to claims 17 and 59, Tyagi teaches hairpin structures (see column 5, lines 1-30).

With regard to claims 21 and 22, Tyagi teaches FAM and TAMRA (see table 1, column 6 and column 8, lines 14-25).

With regard to claims 76, 78, 80, 81, 83, 84, Tyagi teaches the use of FAM (see table 1, column 6 and column 8, lines 14-25 and claim 24).

6. Claims 10-15, 17-22, 47, 59, 66, 67, 76, 78, 80, 81, 83 and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of:

a) providing a first and second primer wherein said the primers are suitable for PCR (see figure 1).

b) hybridizing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule and in the presence of a polymerase under PCR conditions (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4),

c) denaturing the strands and incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template by PCR (page 2518, column 1 and figure 1),

c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) where the DABCYL and FAM labels are not a FRET pair.

With regard to claims 10, 20 and 47, Nazarenko teaches a primer which hybridizes to a target where the primer comprises a detectable label, fluorescein, which is located only internally (see table 1, page 2517, where fluorescein is located internally. If Applicant argues that the oligonucleotide also has a DABCYL at the 5' end, since DABCYL is not fluorescent chromophore, it is not a "detectable" label. This is further supported by the specification which specifically refers to DABCYL as a quenching agent at page 23 and defines a label as any moiety which undergoes a detectable change upon hybridization and/or extension at page 44, both of which result in DABCYL not being a label).

With regard to claim 11-12, 14-15, Nazarenko teaches analysis during PCR (see figure 1).

With regard to claim 13, Nazarenko teaches the use of Fluorescein (see table 1).

With regard to claim 17, 19, Nazarenko teaches hairpin structures (see table 1).

With regard to claim 19, Nazarenko teaches a hairpin (see table I).

With regard to claim 21, Nazarenko teaches fluorescein (see page 2517, table 1).

With regard to claims 56-62, Nazarenko teaches labels "near" the 3' or 5' termini (see table 1).

With regard to claims 66-67, Nazarenko teaches labels within 10 nucleotides of the 3' end (see table 1).

With regard to claims 76, 78, 80, 81, 83, 84, Nazarenko teaches the use of FAM (see page 2517, table 1).

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of:

a) providing a first and second primer wherein said the primers are suitable for PCR (see figure 1).

b) hybridizing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule and in the presence of a polymerase under PCR conditions (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4),

c) denaturing the strands and incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template by PCR (page 2518, column 1 and figure 1),

c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) where the DABCYL and FAM labels are not a FRET pair.

With regard to claims 10, 20 and 47, Nazarenko teaches a primer which hybridizes to a target where the primer comprises a detectable label, fluorescein, which is located only internally (see table 1, page 2517, where fluorescein is located internally. If Applicant argues that the oligonucleotide also has a DABCYL at the 5' end, since DABCYL is not fluorescent chromophore, it is not a "detectable" label. This is further supported by the specification which specifically refers to DABCYL as a quenching

agent at page 23 and defines a label as any moiety which undergoes a detectable change upon hybridization and/or extension at page 44, both of which result in DABCYL not being a label).

With regard to claim 11-12, 14-15, Nazarenko teaches analysis during PCR (see figure 1).

With regard to claim 13, Nazarenko teaches the use of Fluorescein (see table 1).

With regard to claim 17, 19, Nazarenko teaches hairpin structures (see table 1).

With regard to claim 19, Nazarenko teaches a hairpin (see table I).

With regard to claim 21, Nazarenko teaches fluorescein (see page 2517, table 1).

With regard to claims 59, Nazarenko teaches labels "near" the 3' or 5' termini (see table 1).

With regard to claims 66-67, Nazarenko teaches labels within 10 nucleotides of the 3' end (see table 1).

Nazarenko does not teach each possible location of the internal base.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

10. Claims 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (U.S. Patent 6,150,097).

Tyagi teaches a method of claims 10, 20, 47 for quantification of target nucleic acid molecules in a sample comprising hybridizing labeled oligonucleotides with the target molecules and quantifying the amount of the target nucleic acid molecules (see column 9, lines 31-57),

Wherein said one or more oligonucleotides comprise one or more detectable labels located only internally (see column 7, lines 23-30, where Tyagi states "another configuration that should be useful is to separate the label moieties by five nucleotides along the stem hybrid")

And said one or more labels undergo a detectable change in an observable property upon said hybridizing (see column 5 and example 3)

Wherein said detectable change is not the result of a fluorescence resonance energy transfer (see column 5, lines 56-62 and title "Nucleic acid probes having Non-FRET fluorescence quenching").

With regard to claims 11-12, 14-15, Tyagi teaches placement of the Non-FRET molecular beacons in a PCR amplification reaction and measurement during the PCR reaction(see column 14, lines 19-62).

With regard to claims 13, Tyagi teaches fluorescent labels (see Table I, column 6).

With regard to claims 17 and 59, Tyagi teaches hairpin structures (see column 5, lines 1-30).

With regard to claims 21 and 22, Tyagi teaches FAM and TAMRA (see table 1, column 6 and column 8, lines 14-25).

With regard to claims 56-58, 60-62, Tyagi teaches compositions with two labels on the stem hybrid (see column 7, lines 23-30) where one of the labels will be "nearer" to the 3' or 5' end than the other label (which will be nearer the other end).

Tyagi does not teach each possible location of the internal base.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

11. Claims 76-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521) in view of Lee et al (U.S. Patent 5,945,526).

Nazarenko teaches the limitations of claim 20 as discussed above.

Nazarenko does not teach the use of ROX and JOE.

Lee teaches the use of labels like JOE and ROX (see column 23, lines 12-37).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention to use the labels of Lee in the method of Nazarenko since Lee teaches that these dyes are desirable dyes relative to other dyes which have broader emission patterns (see column 3, lines 12-25). Lee specifically notes "As illustrated in Example 4 and FIG. 2, energy transfer dyes such as 5-TMR-B-CF, which include a donor, acceptor and linker as specified above exhibit enhanced fluorescence as compared to the acceptor itself and energy transfer fluorescent dyes having the same donor--acceptor pair where the linker between the donor--acceptor pair is different. (see column 29, lines 35-50)." So an ordinary practitioner, desiring enhanced fluorescence and a desirable dye, would have selected ROX and JOE. Further, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the

mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

12. Claims 76-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al (U.S. Patent 6,150,097) in view of Lee et al (U.S. Patent 5,945,526).

Tyagi teaches the limitations of claim 20 as discussed above.

Tyagi does not teach the use of ROX and JOE.

Lee teaches the use of labels like JOE and ROX (see column 23, lines 12-37).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention to use the labels of Lee in the method of Tyagi since Lee teaches that these dyes are desirable dyes relative to other dyes which have broader emission patterns (see column 3, lines 12-25). Lee specifically notes "As illustrated in Example 4 and FIG. 2, energy transfer dyes such as 5-TMR-B-CF, which include a donor, acceptor and linker as specified above exhibit enhanced fluorescence as compared to the acceptor itself and energy transfer fluorescent dyes having the same donor--acceptor pair where the linker between the donor--acceptor pair is different. (see column 29, lines 35-50)." So an ordinary practitioner, desiring enhanced fluorescence and a desirable dye, would have selected ROX and JOE. Further, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components

at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Response to Arguments

13. Applicant's arguments filed February 22, 2005 have been fully considered but they are not persuasive.

Applicant argues that Tyagi and Nazarenko teach two types of detectable labels and therefore do not anticipate or render obvious the current claims. This argument is not persuasive because the interpretation of "single type" is not limited to an interpretation which excludes the methods of Tyagi and Nazarenko. As noted in the claim interpretation heading above, a "single type" of molecule may refer to molecules that share the common function of performing in a fluorescence assay. Another interpretation would be that a "single type" of molecules are structurally or functionally similar, such as two fluorophores which share the common property of being capable of being excited (as in Tyagi).

The dictionary definition of the term "type" is "A number of people or things having in common traits or characteristics that distinguish them as a group or class (see dictionary.com)." So a single type is a single set of things with common traits or characteristics. The labels of both Tyagi and Nazarenko share common traits and characteristics, including ability to absorb electromagnetic energy most significantly, and participate in fluorescent detection modalities. Therefore, using the dictionary definition,

as well as the definition as understood by the skilled practitioner, Tyagi and Nazarenko meet the limitation of a "single type".

Since the arguments are not persuasive, the rejection is maintained.

Conclusion

14. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
3/30/05